UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trad mark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

HA

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/361,576	07/27/99	STOCKWELL B	2001180-0028

HM22/0911

BRENDA HERSCHBACH JARRELL
CHOATE HALL & STEWART
EXCHANGE PLACE
53 STATE STREET
BOSTON MA 02109-2891

EXAMINER	
PRASTHOFER, T	
ART UNIT	**PAPER NUMBER**
1627	17

DATE MAILED: 09/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No. 09/361,576	Applicant(s) Stockwell et al.
	Examiner First Last	Art Unit 1234

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 8, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *39-56* is/are pending in the application.

4a) Of the above, claim(s) *39, 40, 52, and 54-56* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *41-51 and 53* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. A Petition Under 37 C.F.R. 1.136 received September 5, 2000 and Response to Official Action Under 37 C.F.R. 1.111 was entered as Paper Nos. 15-16.

Status of Claims

2. Claims 41-56 (newly added) are pending in the instant application.

3. Claims 41-51 and 53 are under examination in the instant application.

4. Claims 1-38 are cancelled as per applicant's May 4, 2000 and June 8, 2001 requests.

5. Claims 39-40, 52 and 54-56 are withdrawn from further consideration by the Examiner under 37 C.F.R. 1.142(b), as being drawn to a non-elected inventions, the requirement having been traversed in Paper No. 13.

Response to the June 8, 2001 Amendment Response to Official Action Under 37 C.F.R. 1.111

For the record, it is noted that applicants': [1] have received a December 5, 2000 action on the merits for the originally claimed invention; and that [2] arguments as set forth in applicants' June 8, 2001 Amendment have been directed to the claims **as amended** and not to the claims as originally presented for examination in the December 5, 2000 Office Action.

6. Applicants' arguments filed in the June 8, 2001 Amendment have been fully considered and discussed below, under each corresponding section heading.

~~7. The text of those sections of Title 35, U.S. Code not included in this action can be found~~ in a prior Office action.

Election By Original Presentation

8. Newly submitted claims 52 and 54-56 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

[a] the originally presented and elected claims 1-25 of Group I, without traverse in Paper Nos. 9 and 11 (now canceled at applicants' request) are directed to:

methods of screening chemical compounds, comprising providing an assay format containing a plurality of reaction vessels arranged with sufficient density that individual vessels are separated from one another by no more than about 5 millimeters; introducing at least one chemical compound into each of said plurality of reaction vessels; introducing an assay system capable of undergoing at least one chemical or biological reaction into each of said plurality of reaction vessels; and detecting an effect of at least one of the chemical compounds on the chemical or biological reaction;

[b] while, new claims 52 and 54-56, dependent from new claims 41-42 are directed to methods for screening a library of test compounds further comprises

"wherein in the step of introducing a ligand into each reaction vessel, the ligand ins an antibody (as in claim 52)"

introducing a second ligand and washing away unbound ligands, and wherein the step of measuring comprises measuring levels of ligand comprises measuring levels of ligand comprises measuring levels of second ligand (as in claim 54);

wherein the second ligand is an antibody (as in claim 55);

wherein the second ligand is an antibody conjugated to horseradish peroxidase, and wherein the levels of the second ligand are detected by detecting levels of radiation, fluorescence or chemiluminescence (as in claim 56).

Note that originally elected claims 1-25 of Group I for prosecution do not refer to the use of second ligands, any associated steps of binding said second ligands, wherein the aforementioned second ligand is an antibody, antibody conjugated to horseradish peroxidase, and wherein the levels of the second ligand are detected by detecting levels of radiation, fluorescence or chemiluminescence.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claim 54-56 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and MPEP § 821.03.

Withdrawn Objection(s) and/or Rejection(s)

9. The rejection of claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in light of applicant's amendments.

10. The rejection of claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections are withdrawn in light of applicant's amendments.

Outstanding Objection(s) and/or Rejection(s)

11. **Note that all of the following are rejections under 35 U.S.C. § 103 (a) are maintained for the following reasons of record.**

For applicant's convenience, the following rejections are reiterated below in their entirety, which are followed by the Examiner's comments with regard to applicant's June 8, 2001 Response.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Gallop et al. (U.S. Patent No. 5,525,734, Filed: June 22, 1994, Issued: June 11, 1996), Manns (U.S. Patent No. 4,948,442, Filed June 18, 1995, Issued August 14, 1990), applicants' admission (see, instant specification, page 29, lines 6-19), F.F. Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

Gallop et al. teaches: [1] methods for synthesizing and screening pyrrolidine compound libraries via in situ incorporation on a plurality of solid supports or reaction vessels (see, abstract, col. 3, lines 60-67 to col. 4, lines 1-7); [2] that the aforementioned library compounds, such that one unique or single compound per reaction vessel, are screened for biological or pharmaceutical activity (see, col. 4, lines 30-51 and col. 5, lines 41-45) to isolate individual compounds that bind to a receptor (i.e. undergo a biological or chemical reaction) or possess some desired property (see, col. 3, lines 39-41); i.e, such compounds have diverse pharmaceutical and chemical properties/utilities, that include acting as anti-hyperintensive agents, inhibitors of angiotensin-converting enzyme or are included as a central core of biologically active alkaloids or in peptide compounds having receptor binding activity; [3] that the solid supports used herein include other conventional forms (see, col 5, lines 65-68 to col. 6, lines 1-9, esp. col. 6, line 7) or are described in either WO 93/06121 or in the solid supports described in U.S. Patent No. 5,143,854 to screen compounds for binding affinity to ligands (see, col. 3, lines 53-59 and col. 5, lines 65-67 to col. 6, lines 1-9).

In view of the above, Gallop et al. ***differs*** from the claimed invention in that it ***does not teach*** the screening of chemical compounds in an assay format containing a plurality of reaction vessels, which are:

[1] separated from one another by no more than about 5 millimeters;

[2] separated from one another by no more than about 2 millimeters;

[3] that said assay vessel contain at least 100 reaction vessels; and/or

[4] wherein the volume of each reaction vessel is less than or equal to approximately 200 microliters

However, it is conventionally known in the art that assay formats, such as microtiter plates: [a] while commonly used in the standardized form of a multi-well filter apparatus that provides at least 96 depressions or cylindrical wells (see, Manus, col. 1, lines 13-18); [b] it is known "configurations of such assay formats or plates depend upon the wishes of the designer or user (see, Manus, col. 3, lines 53-55)", such configurations include, increasing or decreasing number of wells, materials used in construction, design and structural components of such plates or reaction vessels, including arrangements of, spacing between each well shape or depth (i.e, to be cylindrical, conical), well sample volume; [c] that such plates may be a removable, disposable, or detachable unit for further processing (see, col. 2, lines 45-52) and that such apparatus are commonly used to prepare libraries in microtiter plates via automation or robotics or otherwise (see, Manus, col. 3, lines 53-55 and Craig et al., page 404, lines 1-11); [d] "denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 96 well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. Still denser plates, such as the 6144 well plates . . .are particularly preferred. An ideal assay for high throughput screening would be compatible with any or all of these array formats (see, instant specification, page 29, lines 6-19); and [e] high throughput screening results in the testing of many samples against a number of biological targets

of interest that include compounds derived by automated or manual methods (see, page 399, abstract and lines 1-11 and Craig, p. 401, lines 34-37 to p. 402 to 403) (also see generally, F.F. Craig, "Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

A person of ordinary skill in the art would have been motivated to screen pyrrolidine compounds and/or corresponding compound libraries as taught by Gallop et al. via different assay formats, because the aforementioned compounds and/or corresponding compound libraries as taught by Gallop et al. have diverse pharmaceutical and chemical properties/utilities, etc. it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success in screening or identifying pharmaceutical pyrrolidine compounds via the use of different assay formats, such as well plate apparatus, because [1] Gallop et al. teaches that synthetic methods for the preparation of pyrrolidine libraries on solid supports and that such compounds have diverse pharmaceutical and chemical properties/utilities; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

It would have been ***prima facie*** **obvious** to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Gallop et al. with the teachings of what is conventionally known in the art as taught by Manus and Craig to use different assay formats as adapted to the needs or "wishes of the designer or user" based upon experimental necessity.

18. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zambias et al. (U.S. Patent No. 5,736,412, Filed: May 17, 1996, Issued: April 7, 1998), Manns (U.S. Patent No. 4,948,442, Filed June 18, 1995, Issued August 14, 1990), applicants' admission (see, instant specification, page 29, lines 6-19), applicants' admission (see, instant specification, page 29, lines 6-19), and F.F. Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

Zambias et al. teaches: [1] a method directed to the synthesis and/or screening of an array of different organic chemical compounds (see, col. 12, lines 4-7), with a common molecular core structure (see, abstract, col. 9, line 52 and col. 5, lines 31-37); [2] which comprises (see, col. 13, lines 16-18 and 24-25): (a) simultaneous screens for assaying large numbers of parallel compound samples (see, col. 5, lines 1-3) with different structures, functionalities and spatial arrangements for exploring biological activity (see, col. 12, lines 4-7 and examples cols.15-16), such as for use as drug candidates (see col. 11, lines 59-67) in microtiter plates (see, Figure on front of patent); (b) the steps of (1) placing a set of building blocks A in a solvent; (2) mixing the building blocks of A with additional building blocks B; and then mixing the aforementioned solutions with building blocks C in a different solvents, etc. yielding desired products; (3) in which those product

samples are subject to standard organic spectroscopic analysis (see, col. 6, lines 6-21), such as high performance liquid chromatography ("HPLC"), and each sample is analyzed via the removal of aliquot samples from each respective microtiter plate wells (see, also table 4, an expanded view of a single reaction plate layout/template array, col 33, lines 1-20); and [5] to optimize results this method incorporates use of known chemical and physical properties important to set reaction conditions, (i.e., sets of paralogs are constructed by systematically varying five independent parameters: 1 a hydrophobic index; an isoelectric point derived from overall charge by averaging pka and pH values, a hydrophobic moment, an analogous dipole moment, a corrugation factor, etc., See, col. 5, lines 16-30).

In view of the above, Zambias et al. ***differs*** from the claimed invention in that it ***does not teach*** the screening of chemical compounds in an assay format containing a plurality of reaction vessels, which are:

[1] separated from one another by no more than about 5 millimeters;

[2] separated from one another by no more than about 2 millimeters;

[3] that said assay vessel contain at least 100 reaction vessels;

[4] wherein the volume of each reaction vessel is less than or equal to approximately 200 microliters

However, it is conventionally known in the art that assay formats, such as microtiter plates: [a] while commonly used in the standardized form of a multi-well filter apparatus that provides at least 96 depressions or cylindrical wells (see, Manus, col. 1, lines 13-18);

[b] it is known "configurations of such assay formats or plates depend upon the wishes of the designer or user (see, Manus, col. 3, lines 53-55)", such configurations include, increasing or decreasing number of wells, materials used in construction, design and structural components of such plates or reaction vessels, including arrangements of, spacing between each well shape or depth (i.e, to be cylindrical, conical), well sample volume; [c] that such plates may be a removable, disposable, or detachable unit for further processing (see, col. 2, lines 45-52) and that such apparatus are commonly used to prepare libraries in microtiter plates via automation or robotics or otherwise (see, Manus, col. 3, lines 53-55 and Craig et al., page 404, lines 1-11); [d] "denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 96 well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. Still denser plates, such as the 6144 well plates . . .are particularly preferred. An ideal assay for high throughput screening would be compatible with any or all of these array formats (see, instant specification, page 29, lines 6-19); and [e] high throughput screening results in the testing of many samples against a number of biological targets of interest that include compounds derived by automated or manual methods (see, page 399, abstract and lines 1-11 and Craig, p. 401, lines 34-37 to p. 402 to 403) (also see generally, F.F. Craig, "Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404);

A person of ordinary skill in the art would have been motivated to screen chemical compounds and/or corresponding compound libraries as taught by Zambias et al. via different assay formats, because the aforementioned compounds and/or corresponding compound libraries as taught by Zambias et al. have diverse pharmaceutical and chemical properties/utilities, etc. it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success in screening or identifying pharmaceutical pyrrolidine compounds via the use of different assay formats, such as well plate apparatus, because [1] Zambias et al. teaches that synthetic and screening methods of chemical compounds and/or libraries that have diverse pharmaceutical and chemical properties/utilities; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

It would have been ***prima facie*** **obvious** to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Zambias et al. with the teachings of what is conventionally known in the art as taught by Manus and Craig to use different assay formats as adapted to the needs or "wishes of the designer or user" based upon experimental necessity.

19. Claims 1-2, 5-6, 9-10, 13-14, 18-19 and 22-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Godowski et al. (U.S. Patent No. 6,025,145, Filed: January 20, 1995 (371 Date), PCT Filed: November 18, 1994 (PCT Priority), Issued: February 15, 2000), Manns (U.S. Patent No. 4,948,442, Filed June 18, 1995, Issued August 14, 1990), applicants' admission (see, instant specification, page 29, lines 6-19), applicants' admission (see, instant specification, page 29, lines 6-19), and F.F. Craig ("Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).

Godowski et al. teaches: [1] an kinase receptor activation (KIRA) assay for measuring activation (i.e., autophosphorylation, which is involved in a mechanism of signal transduction in animals) of a tyrosine kinase receptor of interest (see, abstract), wherein ; [2] wherein said assay is a high throughput assay for the evaluation of large numbers of sample test compound ligands, agents etc. and is used for measuring autophosphorylation of the kinase domain of a receptor protein tyrosine kinase (rPTK) using a kinase receptor activation, enzyme-linked immunosorbent assay (KIRA ELISA) (see, col. 1, lines 12-17) and enables identification of agonist and antagonist ligands for the tyrosine receptor of interest; [3] wherein said assay system is conducted in an microtiter plate containing wells, such that: [a] in a first step: a first solid phase (e.g., a/each well of a first assay plate) is coated with a substantially homogeneous population of cells (i.e., usually a mammalian cell line or eukaryotic cell line) so that the cells adhere to the first solid phase (i.e, the cells have either an endogenous tyrosine kinase receptor or have been transformed with DNA encoding a receptor or "receptor construct" and the DNA has been expressed so that the receptor

or receptor construct is presented in the cell membranes of the cells) (see, col. 4, lines 55-59); [b] in a second step: a ligand or analyte is then added to the solid phase having the adhering cells, such that the tyrosine kinase receptor is exposed to the ligand (in each well); [c] Following exposure to the ligand, the adherent cells are solubilized, thereby releasing cell lysate.; [d] A second solid phase is coated with a capture agent which binds specifically to the tyrosine kinase receptor, or, in the case of a receptor construct to the flag polypeptide.; [e] The cell lysate obtained in step c) is added to the wells containing the adhering capture agent so as to capture the receptor or receptor construct to the wells. (i.e., ELISA component of the assay system (see, col.; 5, lines 51-68, to col. 6, lines 1-24); [f] A washing step is then carried out, so as to remove unbound cell lysate, leaving the captured receptor or receptor construct.; [g] The captured receptor or receptor construct is exposed to a labeled anti-phosphotyrosine antibody which identifies phosphorylated residues in the tyrosine kinase receptor.; and [h] Binding of the anti-phosphotyrosine antibody to the captured receptor or receptor construct is measured.

In view of the above, Godowski et al. ***differs*** from the claimed invention in that it ***does not teach*** the screening of chemical compounds in an assay format containing a plurality of reaction vessels, which are:

[1] separated from one another by no more than about 5 millimeters;

[2] separated from one another by no more than about 2 millimeters;

[3] that said assay vessel contain at least 100 reaction vessels;

[4] wherein the volume of each reaction vessel is less than or equal to approximately 200 microliters

However, it is conventionally known in the art that assay formats, such as microtiter plates: [a] while commonly used in the standardized form of a multi-well filter apparatus that provides at least 96 depressions or cylindrical wells (see, Manus, col. 1, lines 13-18); [b] it is known "configurations of such assay formats or plates depend upon the wishes of the designer or user (see, Manus, col. 3, lines 53-55)", such configurations include, increasing or decreasing number of wells, materials used in construction, design and structural components of such plates or reaction vessels, including arrangements of, spacing between each well shape or depth (i.e, to be cylindrical, conical), well sample volume; [c] that such plates may be a removable, disposable, or detachable unit for further processing (see, col. 2, lines 45-52) and that such apparatus are commonly used to prepare libraries in microtiter plates via automation or robotics or otherwise (see, Manus, col. 3, lines 53-55 and Craig et al., page 404, lines 1-11); [d] "denser arrays are generally preferred, though it is appreciated that such arrays may desirably have the same external dimensions of a standard 96 well plate in order to facilitate automation using available equipment. Plates containing 384 (Nalge Nunc International, Naperville, IL; Greiner America, Lake Mary, FL) wells have recently become commercially available and may be used in the practice of the present invention. Still denser plates, such as the 6144 well plates . . .are particularly preferred. An ideal assay for high throughput screening would be compatible with any or all of these array formats (see, instant specification, page 29, lines 6-19); and [e] high throughput screening results in the testing of many samples against a number of biological targets of interest that include compounds derived by automated or manual methods (see, page 399, abstract and lines 1-11 and Craig, p. 401, lines 34-37 to p. 402 to 403) (also see generally, F.F.

Craig, "Chapter 14, Screening Combinatorial Libraries," A Practical Guide to Combinatorial Chemistry, Czarnik and DeWitt, eds., Washington, D.C.: American Chemical Society, 1997, 404).;

A person of ordinary skill in the art would have been motivated to screen agonist and antagonist ligands as taught by Godowski et al. via different assay formats, because [1] Godowski teaches that an kinase receptor activation (KIRA) assay for measuring autophosphorylation, which is involved in a mechanism of signal transduction in animals, of a tyrosine kinase receptor of interest and enables identification of agonist and antagonist ligands for the tyrosine receptor of interest; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

In light of the foregoing, a person of ordinary skill in the art would have had a reasonable expectation of success in screening or identifying pharmaceutical pyrrolidine compounds via the use of different assay formats, such as well plate apparatus, because [1] Godowski teaches that an kinase receptor activation (KIRA) assay for measuring autophosphorylation, which is involved in a mechanism of signal transduction in animals, of a tyrosine kinase receptor of interest and enables identification of agonist and antagonist ligands for the tyrosine receptor of interest; and [2] it is conventionally known in the art that assay formats, such as microtiter plate or wells are readily adaptable and made to the needs of the designer or used for specific purposes as nessitated by

experiment, which may include uses as biological assays or screening, as taught by Manus and F.F. Craig.

It would have been ***prima facie*** **obvious** to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Godowski et al. with the teachings of what is conventionally known in the art as taught by Manus and Craig to use different assay formats as adapted to the needs or "wishes of the designer or user" based upon experimental necessity.

In the September 5, 2000 Response, applicants assert that:

[1] the burden of establishing a prima facie case of obviousness has not been met because there is no suggestion or motivation to combine the references, in that:

[a] each of the aforementioned references do not teach the claimed invention; and the combination of those references also do not teach the claim limitations of the instant invention;

[b] an improper "obvious to try" rationale has been applied in support of the above-identified rejections; and

[2] in light of the foregoing requests that aforementioned rejections be withdrawn.

In response, it is the position of the Examiner that:

[1] Applicants' arguments have been carefully considered, but found unpersuasive. It is noted again that substantially similar arguments were made previously on the record and are still applicable.;

[a] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In the instant case, the combined teaching of the aforementioned references teaches the specific combination of parameters and guidance for the use of or renders obvious the claimed invention as there is no reasonable indication that a product of biological processes could not be detected at small volume levels if the art indicates that such screening levels allow for the detection of test compounds at varying volume concentrations.

In light of the above, the rejection is maintained for reasons of record.

New Rejections

New Grounds of Rejection

12. The following rejections are necessitated in light of Applicant's amendments.

New Matter

13. Claims 41-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The added material of new amended claims 41-53 which is not supported by the original disclosure is as follows: the specification **does not teach** the recitation of the terms:

[1] "***a library*** of test compounds" (claims 41 and 42);

[2] "providing ***a library*** of test compounds ***to be assayed for effects on a biological process in the cells***, wherein the biological process is characterized in that ***production of an intracellular product indicates activity of the process***" (claims 41 and 42)";

[3] "***introducing the cells and test compounds*** into the plurality of reaction vessels, wherein ***each reaction vessel contains a subset of the library of test compounds***" (claims 41 and 42);

[4] "contacting the test compounds with the cells for a period of time and ***under conditions sufficient*** for the ***test compounds to exert an effect on the biological process so that levels of the intracellular product are affected"*** (claims 41 and 42);

[5] "***washing away unbound ligands***" (claims 41 and 42);

[6] "wherein in the step of introducing the cells and the test compounds into the plurality of reaction vessels, **each reaction vessel contains an average of one test compound from the library of test compounds**" (claim 51)

[7] "wherein the step of measuring comprises measuring levels of ligand which bound to the biological component ***by measuring levels of photo emissions*** (claim 53)"

[8] "wherein before the step of measuring, ***the method further comprises introducing a second ligand that binds specifically to the ligand and washing away unbound second ligands and wherein the step of measuring comprises measuring levels of ligand comprises measuring levels of the second ligand*** (as in claim 54)"

Accordingly, there is lack of descriptive support for the above-identified terms, wherein the components, substituents, elements, etc. of the claimed invention are other than those recited supra.

In accordance with M.P.E.P. Section 714.02, applicants should specifically point out support for any amendments made to the instant disclosure.

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 41-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

[1] screening strategies associated with the following different classes of chemical compounds as affecting aspects of the cell cycle, as indicated by these examples from the instant specification:

[a] Example 6: screen for small molecule suppressors of antiproliferative agents, demonstrated in the cytoblot assay by the simultaneous treatment of mink lung cells with rapamycin and excess FK506, resulting in the ability of cells to incorporate BrdU; wherein said antiproliferative agents are TGF-B, hydroxyurea, nocodazole, minosine, benomyl, trapoxin, trichostatin and depudicin (see, instant specification page 61-62);

[b] Example 7: screen for natural products suppressors of anti-proliferative agents, obtained from specific marine sponge extracts demonstrated in the cytoblot assay by the simultaneous treatment of mink lung cells with rapamycin and excess FK506, resulting in the ability of cells to incorporate BrdU; wherein said antiproliferative agents, cytostatic proteins or small molecules selected from are TGF-B, hydroxyurea, nocodazole, minosine, benomyl, trapoxin, trichostatin and depudicin and DNA-damaging agents: mitomycin, bleomycin, cisplatin, UV light and gamma irradiation (see, instant specification page 62-63);

[c] Example 9: assaying small molecule suppressors of cell-cycle arresting agents with jugalone, trapoxin and camptothecin (see, instant specification, pages 63-64 ;

[d] Example 10: assaying small molecule suppressors of G-2 arresting agents with purine analogs (see, instant specification, page 65); and

[e] Example 11: use of inventive cytoblot to identify compounds of Formula (1); Formula (20); Formula (30); Formula (40), Formula (50), Formula (60) (see, instant specification at pages 73-81) that alter progression through the mammalian cell cycle, of interfering with the cytoskeletal structure of cells undergoing mitosis (see, instant specification at pages 65-81).

but the specification does not reasonably provide enablement for method for screening ***all*** libraries of ***all*** test compounds with effects on ***all*** biological processes in ***all*** cells, comprising the steps of . . . providing a plurality of ***all*** cells; providing ***all*** libraries of ***all*** test compounds to be assayed for ***all*** biological processes in ***all*** cells, wherein all biological processes are characterized in that production of ***all*** intracellular products indicate activities of ***all*** of the aforementioned processes . . . wherein each reaction vessel contains ***a/all*** subset(s) of ***all*** libraries of ***all*** test compounds, contacting ***all*** test compounds with ***all*** cells for ***all*** periods of time and under ***all*** conditions sufficient for ***all*** test compounds to exert and effect on ***all*** biological processes so that ***all*** levels of ***all*** intracellular products are affected, introducing into each reaction vessel ***all*** ligands that bind specifically ***all*** intracellular products in ***all*** biological processes so that ***all*** ligands bind to ***all*** products . . ., etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

16. Claims 41-42 and 53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claims 41 and 42 are vague and indefinite in that the following terms are not defined in the preamble of those claims:

[1] "a library of test compounds to identify those compounds with effects on a biological process in cells"; it is unclear what that term refers to, as the metes and bounds of the

aforementioned claim cannot be determined as the specification, claims and art do not recognize what the generic terms "library of test compounds" and to "identify those compounds with effects on a biological process in cells" defines as the claims fail to define what compound libraries are tested and by what testing means are used to identify which compound members effectuates what biological processes in what cell types? Applicant is requested to point to where in the specification that those terms are defined. Clarification is requested.

[2] "wherein the biological process is characterized in that production of an intracellular product indicates activity of the process"; it is unclear what that term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what those generic terms mean as the claims fail to define what "biological process is characterized" and what "intracellular product would be indicative of the activity of such a process." Applicant is requested to point to where in the specification that those terms are defined. Clarification is requested.

[3] "contacting the test compounds with the cells for a period of time and under conditions sufficient for the test compounds to exert an effect on the biological process so that levels of the intracellular product are affected"; it is unclear what that term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what those generic terms mean as the claims fail to define what "conditions are sufficient" and for what "period of time" should the test compounds of the claimed invention be

contacted? Applicant is requested to point to where in the specification that those terms are defined. Clarification is requested.

[4] "measuring levels of ligand which bound to the biological component"; it is unclear what that term refers to, as the metes and bounds of the aforementioned claim cannot be determined as the specification, claims and art do not recognize what those generic terms mean as the claims fail to define how such "levels of ligands are measured?" Applicant is requested to point to where in the specification that those terms are defined. Clarification is requested.

Status of Claims

18. No claims are allowed in the above-identified application.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Grace C. Hsu, Ph.D., J.D., whose telephone number is (703) 308-7005. The Examiner may be reached during normal business hours, Monday through Friday from 8:30 am to 6:00 pm (EST). A message may be left on the Examiner's voice mail.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jythosna Venkat, Ph.D., may be reached at (703) 308-2439. The fax number assigned to Group 1627 is (703) 305-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1627 receptionist whose telephone number is (703) 308-0196.

Grace C. Hsu, Ph.D.
August 30, 2001

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600